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NF-YA underlies EZH2 upregulation and is essential for proliferation of human epithelial ovarian cancer cells

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Abstract

Epithelial ovarian cancer (EOC) accounts for the most gynecologic malignancy-associated deaths in the United States. Enhancer of zeste homolog 2 (EZH2), which silences gene expression through generating trimethylation on lysine 27 residue of histone H3 (H3K27Me3), is often overexpressed in EOCs and has been suggested as a therapeutic target. However, the mechanism underlying EZH2 overexpression in EOCs is unknown. Here, we show that EZH2 is upregulated at the transcription level, and two CCAAT boxes in the proximal regions of the human EZH2gene promoter are critical for its transcription inEOCcells. Indeed, NF-YA, the regulatory subunit of the CCAAT-binding transcription factor NF-Y, is expressed at higher levels in human EOCs than in primary human ovarian surface epithelial (HOSE) cells. In addition, there is a positive correlation between expression of NF-YA and EZH2 in EOCs. Notably, high NF-YA expression predicts shorter overall survival in patients with EOCs. The association of NF-YA with the promoter of the human EZH2 gene is enhanced in human EOC cells compared with primary HOSE cells. Significantly, knockdown of NF-YA downregulates EZH2, decreases H3K27Me3 levels, and suppresses the growth of human EOC cells both in vitro and in a xenograft mouse model. Notably, NF-YA knockdown induces apoptosis ofEOCcells and ectopic EZH2 expression partially rescues apoptosis induced by NF-YA knockdown. Together, these data reveal that NF-Y is a key regulator of EZH2 expression and is required for EOC cell proliferation, thus representing a novel target for developing EOC therapeutics. © 2013 American Association for Cancer Research.

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